L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 362-07-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17β)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Estra-1,3,5(10)-triene-3,17β-diol, 2-methoxy- (7CI, 8CI)
CN Estradiol, 2-methoxy- (6CI)
OTHER NAMES:
CN 2-Hydroxyestradiol 2-methyl ether
CN 2-Methoxyestra-1,3,5(10)-triene-3,17β-diol
CN 2-Methoxyestradiol
CN NSC 659853
CN Panzem
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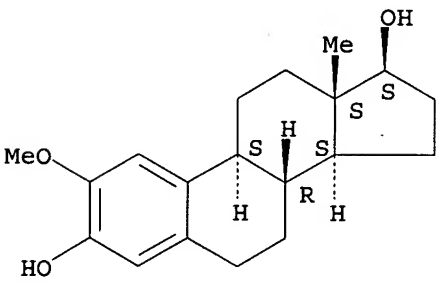
(*File contains numerically searchable property data)

Absolute stereochemistry.



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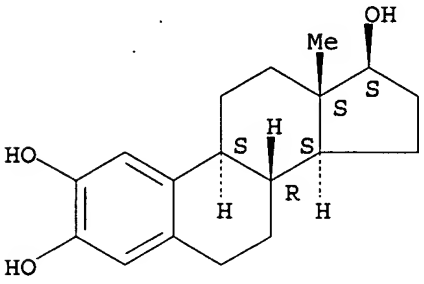
31 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
703 REFERENCES IN FILE CAPLUS (1907 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 362-05-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN Estra-1,3,5(10)-triene-2,3,17-triol, (17β)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Estra-1,3,5(10)-triene-2,3,17β-triol (7CI, 8CI)
OTHER NAMES:
CN 2,3,17β-Trihydroxyestra-1,3,5(10)-triene
CN 2-Hydroxyestradiol
CN NSC 61711
FS STEREOSEARCH
MF C18 H24 O3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



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21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
875 REFERENCES IN FILE CAPLUS (1907 TO DATE)
15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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STRUCTURE FILE UPDATES:   16 MAR 2007  HIGHEST RN 926905-73-9
DICTIONARY FILE UPDATES:  16 MAR 2007  HIGHEST RN 926905-73-9

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> E "2-HYDROXYESTRADIOL"/CN 25
E1            1     2-HYDROXYEQUILIN/CN
E2            1     2-HYDROXYESTRA-1,3,5(10)-TRIEN-17B-OL/CN
E3            1 --> 2-HYDROXYESTRADIOL/CN
E4            1     2-HYDROXYESTRADIOL 1-GLUTATHIONE THIOETHER/CN
E5            1     2-HYDROXYESTRADIOL 17-ACETATE/CN
E6            1     2-HYDROXYESTRADIOL 17-PHOSPHATE/CN
E7            1     2-HYDROXYESTRADIOL 17-SULFATE/CN
E8            1     2-HYDROXYESTRADIOL 2,3-DIMETHYL ETHER/CN
E9            1     2-HYDROXYESTRADIOL 2,3-METHYLENE ETHER/CN
E10           1     2-HYDROXYESTRADIOL 2-GLUCURONIDE/CN
E11           1     2-HYDROXYESTRADIOL 2-METHYL ETHER/CN
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E14           1     2-HYDROXYESTRADIOL 3-BENZOATE/CN
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E17           1     2-HYDROXYESTRADIOL 3-METHYL ETHER GLUTATHIONE THIOETHER/CN
E18           1     2-HYDROXYESTRADIOL 3-SULFATE/CN
E19           1     2-HYDROXYESTRADIOL 4-GLUTATHIONE THIOETHER/CN
E20           1     2-HYDROXYESTRADIOL SULFATE/CN
E21           1     2-HYDROXYESTRADIOL-B-CYCLODEXTRIN INCLUSION COMPD./CN
E22           1     2-HYDROXYESTRADIOL-17B-GLUCURONIDE/CN
E23           1     2-HYDROXYESTRADIOL-4-14C/CN
E24           1     2-HYDROXYESTRADIOL-4-CYSTEINE THIOETHER/CN
E25           1     2-HYDROXYESTRADIOL-6,7-T2/CN

=> S E3
L1            1 2-HYDROXYESTRADIOL/CN

=> DIS L1 1 IDE
THE ESTIMATED COST FOR THIS REQUEST IS 1.95 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   362-05-0  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Estra-1,3,5(10)-triene-2,3,17-triol, (17β)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
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CN Estra-1,3,5(10)-triene-2,3,17β-triol (7CI, 8CI)
OTHER NAMES:
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CN NSC 61711
FS STEREOSEARCH
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CI COM
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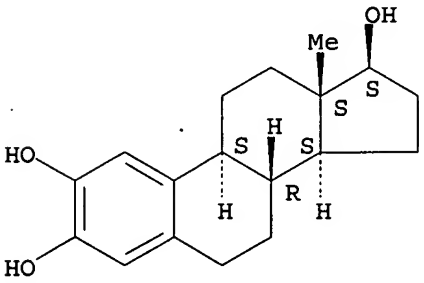
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
875 REFERENCES IN FILE CAPLUS (1907 TO DATE)
15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> E "2-HYDROXYESTRADIOL"/CN 25

E1	1	2-HYDROXYEQUILIN/CN
E2	1	2-HYDROXYESTRA-1,3,5(10)-TRIEN-17B-OL/CN
E3	1 -->	2-HYDROXYESTRADIOL/CN
E4	1	2-HYDROXYESTRADIOL 1-GLUTATHIONE THIOETHER/CN
E5	1	2-HYDROXYESTRADIOL 17-ACETATE/CN
E6	1	2-HYDROXYESTRADIOL 17-PHOSPHATE/CN
E7	1	2-HYDROXYESTRADIOL 17-SULFATE/CN
E8	1	2-HYDROXYESTRADIOL 2,3-DIMETHYL ETHER/CN
E9	1	2-HYDROXYESTRADIOL 2,3-METHYLENE ETHER/CN
E10	1	2-HYDROXYESTRADIOL 2-GLUCURONIDE/CN
E11	1	2-HYDROXYESTRADIOL 2-METHYL ETHER/CN
E12	1	2-HYDROXYESTRADIOL 2-SULFATE/CN
E13	1	2-HYDROXYESTRADIOL 2-SULFATE 17-GLUCURONIDE/CN
E14	1	2-HYDROXYESTRADIOL 3-BENZOATE/CN
E15	1	2-HYDROXYESTRADIOL 3-GLUCURONIDE/CN
E16	1	2-HYDROXYESTRADIOL 3-METHYL ETHER/CN
E17	1	2-HYDROXYESTRADIOL 3-METHYL ETHER GLUTATHIONE THIOETHER/CN
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E19	1	2-HYDROXYESTRADIOL 4-GLUTATHIONE THIOETHER/CN
E20	1	2-HYDROXYESTRADIOL SULFATE/CN
E21	1	2-HYDROXYESTRADIOL-B-CYCLODEXTRIN INCLUSION COMPD./CN
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E25	1	2-HYDROXYESTRADIOL-6,7-T2/CN

=> file caplus

COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 7.35 | 7.56

FILE 'CAPLUS' ENTERED AT 11:18:10 ON 19 MAR 2007
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FILE COVERS 1907 - 19 Mar 2007 VOL 146 ISS 13
FILE LAST UPDATED: 18 Mar 2007 (20070318/ED)

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L2          875 L1

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             12 RENALS
         152799 RENAL
                  (RENAL OR RENALS)
        9025961 DIS?
L3        12770 RENAL(A)DIS?

=> s l2 and l3
L4            5 L2 AND L3

=> d ti au abs so py 1-5
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L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN
TI Estradiol Metabolites Attenuate Renal and Cardiovascular Injury Induced by Chronic Nitric Oxide Synthase Inhibition
AU Tofovic, Stevan P.; Salah, Eman M.; Dubey, Raghvendra K.; Melhem, Mona F.; Jackson, Edwin K.
AB Our previous studies in rodent models of nephropathy demonstrate that 2-hydroxyestradiol (2HE), an estradiol metabolite with little estrogenic activity, exerts reno-protective effects. In vivo, 2HE is readily converted to 2-methoxyestradiol (2ME), a major estradiol metabolite with no estrogenic activity. This study was to determine whether 2ME has renal and cardiovascular protective effects in vivo. First, the acute (90 min) and chronic (14 days) effects of 2ME (10 μg/kg/h) on blood pressure and renal function were examined in normotensive and spontaneously hypertensive rats (SHR). Second, a rat model of cardiovascular and renal injury induced by chronic nitric oxide synthase inhibition (Nω-nitro-L-arginine; 40 mg/kg/d; LNNA group) was used to examine the protective effects of estradiol metabolites. Subsets of LNNA-treated rats were administered either 2HE or 2ME (10 μg/kg/h via osmotic minipump); LNNA+2ME and LNNA+2HE groups, resp. 2-Methoxyestradiol had no acute or chronic effects on blood pressure or renal function in normotensive

animals or on hypertension in SHR. Prolonged, 5-wk NOS inhibition induced severe cardiovascular and renal disease and high mortality (75%, LNNA group). 2ME, but not 2HE, significantly decreased elevated blood pressure and attenuated the reduction in GFR. 2HE delayed the onset of proteinuria, whereas no proteinuria was detected in the 2-ME group. 2HE and 2ME reduced mortality rate by 66% and 83%, resp. ($P < 0.001$). In the kidney, 2HE and 2ME abolished LNNA-induced interstitial and glomerular inflammation, attenuated glomerular collagen IV synthesis, and inhibited glomerular and tubular cell proliferation. In the heart, 2HE and 2ME markedly reduced vascular and interstitial inflammation and reduced collagen synthesis and vascular/interstitial cell proliferation. Thus, in a model of severe cardiovascular and renal injury, 2-methoxyestradiol (a major nonestrogenic estradiol metabolite) exerts renal and cardiovascular protective effects and reduces mortality.

SO Journal of Cardiovascular Pharmacology (2005), 46(1), 25-35
CODEN: JCPCDT; ISSN: 0160-2446

PY 2005

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI 2-Hydroxyestradiol is a prodrug of 2-methoxyestradiol

AU Zacharia, Lefteris C.; Piche, Claude A.; Fielding, Robert M.; Holland, Kathleen M.; Allison, S. Dean; Dubey, Raghvendra K.; Jackson, Edwin K.

AB Previous in vivo studies indicate that 2-hydroxyestradiol (2OHE) attenuates cardiovascular and renal diseases. In vitro studies suggest that the biol. effects of 2OHE are mediated by 2-methoxyestradiol (2MEOE) after methylation of 2OHE by catechol-O-methyltransferase (COMT). This study tested the hypothesis that in vivo 2OHE is a prodrug of 2MEOE. The authors administered to male rats i.v. boluses of either 2OHE or 2MEOE and measured plasma levels of 2OHE and 2MEOE by gas chromatog.-mass spectrometry at various time points after drug administration. After administration of 2OHE, plasma levels of 2OHE declined extremely rapidly [t1/2(1) = 0.94 min and t1/2(2) = 10.2 min] becoming undetectable after 45 min. Concomitant with the disappearance of 2OHE, 2MEOE occurred and then declined [t1/2(1) = 7.9 min and t1/2(2) = 24.9 min]. The peak concentration and total exposure (area under the curve) for 2OHE were much lower than for 2MEOE. 2OHE had a much higher plasma clearance (CL) and volume of distribution (Vd) compared with 2MEOE (2OHE: CL = 1215 mL min-1 kg-1 and Vd = 17,875 mL/kg; 2MEOE: CL = 50 mL min-1 kg-1 and Vd = 1760 mL/kg). After administration of 2MEOE, plasma levels of 2MEOE declined [t1/2(1) = 2.5 min and t1/2(2) = 20.2 min] with a plasma CL of 50 mL min-1 kg-1 and a Vd of 1500 mL/kg. The authors could not detect 2OHE in plasma from rats receiving 2MEOE. The authors conclude that the conversion of 2OHE to 2MEOE is so efficient that in terms of 2MEOE exposure, administration of 2OHE is bioequivalent to administration of 2MEOE itself.

SO Journal of Pharmacology and Experimental Therapeutics (2004), 309(3), 1093-1097
CODEN: JPETAB; ISSN: 0022-3565

PY 2004

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI Administration of estradiol metabolites for the treatment or prevention of obesity, metabolic syndrome, diabetes, and vascular and renal disorders

IN Jackson, Edwin K.; Tofovic, Stevan P.; Dubey, Raghvendra K.

AB Methods are provided for preventing or treating risk factors for cardiovascular disease in an individual, comprising administering a therapeutically effective amount of a composition comprising an estradiol metabolite to said individual. Such risk factors include obesity, the metabolic syndrome, diabetes mellitus, vascular disorders, and renal disorders. Preferred estradiol metabolites include 2-methoxyestradiol, 4- methoxyestradiol, 2-hydroxyestradiol, and 4-hydroxyestradiol or prodrugs thereof. The compns. may also be in the form of a controlled release formulation. Methods are also provided for

use of estradiol metabolites to treat or prevent insulin resistance, vascular endothelial dysfunction, hyperlipidemia, hypertension, diabetic nephropathy, proteinuria and reducing leptin levels. In addition, the methods provide a method of stabilizing glucose levels. These treatments may be used in either gender because of their lack of a feminizing estrogenic effect.

SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2

PY 2003
2004
2003
2003
2006
2004
2005
2005

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI 2-Hydroxyestradiol Attenuates Renal Disease in Chronic Puromycin Aminonucleoside Nephropathy

AU Tofovic, Stevan P.; Dubey, Raghvendra; Salah, Eman M.; Jackson, Edwin K.

AB It has been previously shown that 2-hydroxyestradiol (2-OHE) attenuates the development of renal disease in genetic nephropathy associated with obesity and the metabolic syndrome. The purpose of this study was to test the hypothesis that 2-OHE, irresp. of its effects on metabolic status and/or obesity, exerts direct renoprotective effects in rats in vivo. First, the effects of increasing doses of 2-OHE on mesangial cell growth, proliferation, and collagen synthesis in isolated rat glomerular mesangial cells were evaluated in vitro. Second, the effects of 12-wk administration of 2-OHE (10 μg/h/kg) on renal function and structure in chronic puromycin aminonucleoside (PAN)-induced nephropathy in rats were evaluated in vivo. 2-OHE concentration-dependently (0.001 to 1 M) inhibited serum (2.5%)-induced cell growth (3H-thymidine incorporation), collagen synthesis (3H-proline incorporation), and cell proliferation (cell number). Importantly, the inhibitory effects of 2-OHE (0.1 μM) were not blocked by ICI182780 (50 μM), an estrogen receptor antagonist. In vivo, chronic administration of PAN (75 mg/kg + 5 + 20 mg/kg) over 12 wk induced severe chronic renal disease. Chronic treatment with 2-OHE significantly attenuated PAN-induced decrease in glomerular filtration, reduced proteinuria, and the elevated BP, and it had no effect on PAN-induced increase in plasma cholesterol and triglycerides levels. 2-OHE had no effects on plasma testosterone levels in male nephropathic animals. Immunohistochem. staining for collagen IV and proliferating cell nuclear antigen (PCNA) in glomeruli and transforming growth factor-β (TGF-β) in renal tubular cells were significantly higher in PAN nephropatic rats vs. control animals with intact kidneys. PAN also markedly increased glomerular and interstitial macrophage infiltration (ED1+ cells). 2-OHE had no effects on renal tubular cell TGF-β, but it significantly reduced glomerular PCNA and collagen IV and glomerular and interstitial macrophage infiltration. In summary, this study provides the first evidence that 2-OHE exerts direct renoprotective effects in vivo. These effects are mediated by estrogen receptor-independent mechanisms and are due, at least in part, to the inhibition of some of the key proliferative mechanisms involved in glomerular remodeling and sclerosis.

SO Journal of the American Society of Nephrology (2002), 13(11), 2737-2747
CODEN: JASNEU; ISSN: 1046-6673

PY 2002

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth

AU Xiao, Shen; Gillespie, Delbert G.; Baylis, Christine; Jackson, Edwin K.; Dubey, Raghvendra K.

AB Reduced nitric oxide synthesis by glomerular endothelial cells and increased proliferation of glomerular mesangial cells is associated with glomerular remodeling that leads to accelerated glomerulosclerosis. Estradiol induces nitric oxide synthesis and slows the progression of renal disease. Because the estradiol metabolites 2-hydroxyestradiol and 2-methoxyestradiol are more potent than estradiol in inhibiting growth of vascular smooth muscle cells, which are phenotypically similar to mesangial cells, the authors compared the effects of estradiol, 2-hydroxyestradiol, and 2-methoxyestradiol on growth of glomerular mesangial cells and on basal nitric oxide synthesis by glomerular endothelial cells. In human glomerular mesangial cells, estradiol and its metabolites concentration-dependently (1 nmol/L to 10 μM) inhibited serum (2.5%)-induced DNA synthesis, cell proliferation, and collagen synthesis with the order of potency being 2-methoxyestradiol > 2-hydroxyestradiol > estradiol. ICI182780 (100 μM, an estrogen receptor antagonist) blocked the growth inhibitory effects of estradiol but not 2-hydroxyestradiol or 2-methoxyestradiol. Treatment with estradiol, but not 2-hydroxyestradiol and 2-methoxyestradiol, induced nitric oxide synthesis ($P<0.05$, assayed by the formation of 3H-L-citrulline from 3H-L-arginine) in human glomerular endothelial cells, and these effects were blocked by ICI182780 and L-NMA (a nitric oxide synthesis inhibitor). In conclusion, estradiol may attenuate glomerulosclerosis by inducing nitric oxide synthesis via an estrogen receptor-dependent mechanism and by conversion to 2-hydroxyestradiol and 2-methoxyestradiol, which inhibit glomerular mesangial cell proliferation independent of estrogen receptors.

SO Hypertension (2001), 37(2, Pt. 2), 645-650
CODEN: HPRTDN; ISSN: 0194-911X
PY 2001

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	19.58	27.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.90	-3.90

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STRUCTURE FILE UPDATES: 16 MAR 2007 HIGHEST RN 926905-73-9
DICTIONARY FILE UPDATES: 16 MAR 2007 HIGHEST RN 926905-73-9

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TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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E3            1  --> 2-METHOXYESTRADIOL/CN
E4            1      2-METHOXYESTRADIOL 17-HEMISUCCINATE/CN
E5            1      2-METHOXYESTRADIOL 17-SULFATE/CN
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E23           1      2-METHOXYESTRONE OXIME/CN
E24           1      2-METHOXYESTRONE P-TOSYLHYDRAZONE/CN
E25           1      2-METHOXYESTRONE SULFATE/CN

=> S E3
L5            1 2-METHOXYESTRADIOL/CN

=> DIS L5 1 IDE

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   362-07-2  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Estra-1,3,5(10)-triene-3,17-diol, 2-methoxy-, (17β)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
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CN   2-Methoxyestradiol
CN   NSC 659853
CN   Panzem
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CI   COM
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       IPA, MEDLINE, PHAR, PROMT, PROUSDDR, RTECS*, SPECINFO, SYNTHLINE,
       TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
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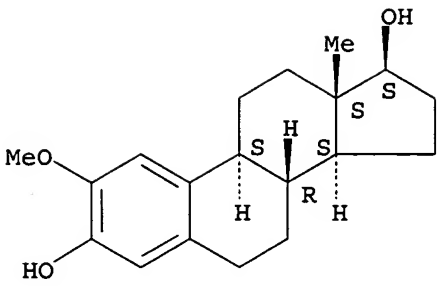

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

701 REFERENCES IN FILE CA (1907 TO DATE)
31 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
703 REFERENCES IN FILE CAPLUS (1907 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.35	34.49

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CA SUBSCRIBER PRICE	0.00	-3.90

FILE 'CAPLUS' ENTERED AT 11:21:02 ON 19 MAR 2007
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FILE COVERS 1907 - 19 Mar 2007 VOL 146 ISS 13
FILE LAST UPDATED: 18 Mar 2007 (20070318/ED)

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(FILE 'HOME' ENTERED AT 11:17:09 ON 19 MAR 2007)

FILE 'REGISTRY' ENTERED AT 11:17:23 ON 19 MAR 2007
E "2-HYDROXYESTRADIOL"/CN 25
L1 1 S E3
E "2-HYDROXYESTRADIOL"/CN 25

FILE 'CAPLUS' ENTERED AT 11:18:10 ON 19 MAR 2007

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L2          875 S L1
L3        12770 S RENAL(A)DIS?
L4            5 S L2 AND L3

     FILE 'REGISTRY' ENTERED AT 11:20:12 ON 19 MAR 2007
                E "2-METHOXYESTRADIOL"/CN 25
L5            1 S E3

     FILE 'CAPLUS' ENTERED AT 11:21:02 ON 19 MAR 2007

=> s l3 and l5
            703 L5
L6            5 L3 AND L5

=> d ti au abs so py 1-5

L6   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   Estradiol Metabolites Attenuate Renal and Cardiovascular Injury Induced by
     Chronic Nitric Oxide Synthase Inhibition
AU   Tofovic, Stevan P.; Salah, Eman M.; Dubey, Raghvendra K.; Melhem, Mona F.;
     Jackson, Edwin K.
AB   Our previous studies in rodent models of nephropathy demonstrate that
     2-hydroxyestradiol (2HE), an estradiol metabolite with little estrogenic
     activity, exerts reno-protective effects.  In vivo, 2HE is readily
     converted to 2-methoxyestradiol (2ME), a major estradiol metabolite with
     no estrogenic activity.  This study was to determine whether 2ME has renal and
     cardiovascular protective effects in vivo.  First, the acute (90 min) and
     chronic (14 days) effects of 2ME (10 μg/kg/h) on blood pressure and
     renal function were examined in normotensive and spontaneously hypertensive
     rats (SHR).  Second, a rat model of cardiovascular and renal injury
     induced by chronic nitric oxide synthase inhibition (Nω-nitro-L-
     arginine; 40 mg/kg/d; LNNA group) was used to examine the protective
     effects of estradiol metabolites.  Subsets of LNNA-treated rats were
     administered either 2HE or 2ME (10 μg/kg/h via osmotic minipump);
     LNNA+2ME and LNNA+2HE groups, resp. 2-Methoxyestradiol had no acute or
     chronic effects on blood pressure or renal function in normotensive
     animals or on hypertension in SHR.  Prolonged, 5-wk NOS inhibition induced
     severe cardiovascular and renal disease and high
     mortality (75%, LNNA group).  2ME, but not 2HE, significantly decreased
     elevated blood pressure and attenuated the reduction in GFR. 2HE delayed the
     onset of proteinuria, whereas no proteinuria was detected in the 2-ME
     group. 2HE and 2ME reduced mortality rate by 66% and 83%, resp. (P <
     0.001).  In the kidney, 2HE and 2ME abolished LNNA-induced interstitial
     and glomerular inflammation, attenuated glomerular collagen IV synthesis,
     and inhibited glomerular and tubular cell proliferation.  In the heart,
     2HE and 2ME markedly reduced vascular and interstitial inflammation and
     reduced collagen synthesis and vascular/interstitial cell proliferation.
     Thus, in a model of severe cardiovascular and renal injury,
     2-methoxyestradiol (a major nonestrogenic estradiol metabolite) exerts
     renal and cardiovascular protective effects and reduces mortality.
SO   Journal of Cardiovascular Pharmacology (2005), 46(1), 25-35
     CODEN: JCPCDT; ISSN: 0160-2446
PY   2005

L6   ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2007 ACS on STN
TI   2-Hydroxyestradiol is a prodrug of 2-methoxyestradiol
AU   Zacharia, Lefteris C.; Piche, Claude A.; Fielding, Robert M.; Holland,
     Kathleen M.; Allison, S. Dean; Dubey, Raghvendra K.; Jackson, Edwin K.
AB   Previous in vivo studies indicate that 2-hydroxyestradiol (2OHE)
     attenuates cardiovascular and renal diseases.  In
     vitro studies suggest that the biol. effects of 2OHE are mediated by
     2-methoxyestradiol (2MEOE) after methylation of 2OHE by
     catechol-O-methyltransferase (COMT).  This study tested the hypothesis
     that in vivo 2OHE is a prodrug of 2MEOE.  The authors administered to male
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rats i.v. boluses of either 2OHE or 2MEOE and measured plasma levels of 2OHE and 2MEOE by gas chromatog.-mass spectrometry at various time points after drug administration. After administration of 2OHE, plasma levels of 2OHE declined extremely rapidly [t1/2(1) = 0.94 min and t1/2(2) = 10.2 min] becoming undetectable after 45 min. Concomitant with the disappearance of 2OHE, 2MEOE occurred and then declined [t1/2(1) = 7.9 min and t1/2(2) = 24.9 min]. The peak concentration and total exposure (area under the curve) for 2OHE were much lower than for 2MEOE. 2OHE had a much higher plasma clearance (CL) and volume of distribution (Vd) compared with 2MEOE (2OHE: CL = 1215 mL min-1 kg-1 and Vd = 17,875 mL/kg; 2MEOE: CL = 50 mL min-1 kg-1 and Vd = 1760 mL/kg). After administration of 2MEOE, plasma levels of 2MEOE declined [t1/2(1) = 2.5 min and t1/2(2) = 20.2 min] with a plasma CL of 50 mL min-1 kg-1 and a Vd of 1500 mL/kg. The authors could not detect 2OHE in plasma from rats receiving 2MEOE. The authors conclude that the conversion of 2OHE to 2MEOE is so efficient that in terms of 2MEOE exposure, administration of 2OHE is bioequivalent to administration of 2MEOE itself.

SO Journal of Pharmacology and Experimental Therapeutics (2004), 309(3), 1093-1097
CODEN: JPETAB; ISSN: 0022-3565
PY 2004

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI Administration of estradiol metabolites for the treatment or prevention of obesity, metabolic syndrome, diabetes, and vascular and renal disorders

IN Jackson, Edwin K.; Tofovic, Stevan P.; Dubey, Raghvendra K.

AB Methods are provided for preventing or treating risk factors for cardiovascular disease in an individual, comprising administering a therapeutically effective amount of a composition comprising an estradiol metabolite to said individual. Such risk factors include obesity, the metabolic syndrome, diabetes mellitus, vascular disorders, and renal disorders. Preferred estradiol metabolites include 2-methoxyestradiol, 4- methoxyestradiol, 2-hydroxyestradiol, and 4-hydroxyestradiol or prodrugs thereof. The compns. may also be in the form of a controlled release formulation. Methods are also provided for use of estradiol metabolites to treat or prevent insulin resistance, vascular endothelial dysfunction, hyperlipidemia, hypertension, diabetic nephropathy, proteinuria and reducing leptin levels. In addition, the methods provide a method of stabilizing glucose levels. These treatments may be used in either gender because of their lack of a feminizing estrogenic effect.

SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
PY 2003
2004
2003
2003
2006
2004
2005
2005

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI Effects of estradiol and its metabolites on glomerular endothelial nitric oxide synthesis and mesangial cell growth

AU Xiao, Shen; Gillespie, Delbert G.; Baylis, Christine; Jackson, Edwin K.; Dubey, Raghvendra K.

AB Reduced nitric oxide synthesis by glomerular endothelial cells and increased proliferation of glomerular mesangial cells is associated with glomerular remodeling that leads to accelerated glomerulosclerosis. Estradiol induces nitric oxide synthesis and slows the progression of renal disease. Because the estradiol metabolites 2-hydroxyestradiol and 2-methoxyestradiol are more potent than estradiol

in inhibiting growth of vascular smooth muscle cells, which are phenotypically similar to mesangial cells, the authors compared the effects of estradiol, 2-hydroxyestradiol, and 2-methoxyestradiol on growth of glomerular mesangial cells and on basal nitric oxide synthesis by glomerular endothelial cells. In human glomerular mesangial cells, estradiol and its metabolites concentration-dependently (1 nmol/L to 10 μM) inhibited serum (2.5%)-induced DNA synthesis, cell proliferation, and collagen synthesis with the order of potency being 2-methoxyestradiol > 2-hydroxyestradiol > estradiol. ICI182780 (100 μM, an estrogen receptor antagonist) blocked the growth inhibitory effects of estradiol but not 2-hydroxyestradiol or 2-methoxyestradiol. Treatment with estradiol, but not 2-hydroxyestradiol and 2-methoxyestradiol, induced nitric oxide synthesis ($P<0.05$, assayed by the formation of 3H-L-citrulline from 3H-L-arginine) in human glomerular endothelial cells, and these effects were blocked by ICI182780 and L-NMA (a nitric oxide synthesis inhibitor). In conclusion, estradiol may attenuate glomerulosclerosis by inducing nitric oxide synthesis via an estrogen receptor-dependent mechanism and by conversion to 2-hydroxyestradiol and 2-methoxyestradiol, which inhibit glomerular mesangial cell proliferation independent of estrogen receptors.

SO Hypertension (2001), 37(2, Pt. 2), 645-650
CODEN: HPRTDN; ISSN: 0194-911X

PY 2001

L6 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2007 ACS on STN

TI Use of anti-angiogenic agents for inhibiting vessel wall injury

IN Brown, Charles L., III; Gorlin, Steve

AB Use of anti-angiogenic agents to inhibit an undesirable response to vessel wall injury, including stent neointima, dialysis graft neointima, vascular graft-induced neointima, and the treatment of benign hypertrophic scar formation as well as the treatment and passivation of unstable atherosclerotic plaques are provided. The invention provides for the use of catheter-based devices for enhancing the local delivery of anti-angiogenic agents into the endothelial tissues of blood vessels of the living body.

SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2

PY 2000
2000
2000

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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3706	nephrotoxic$	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/03/19 10:24
L2	757	estradiol adj metabolite or 2-hydroxyestradiol or 2-methoxyestradiol or 4-hydroxyestradiol or 4-methoxyestradiol	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/03/19 10:26
L3	14	l1 and l2	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:33
L4	3150	proteinur$	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:34
L5	10	l2 and l4	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:43
L6	24680	glomerul$	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:43
L7	102	l2 and l6	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:48
L8	3	l2 same l6	US-PGPUB; USPAT; EPO; JPO; DERWENT	SAME	ON	2007/03/19 10:43
L9	12118	renal adj disease or renal adj disorder	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2007/03/19 10:48
L10	24	l2 and l9	US-PGPUB; USPAT; EPO; JPO; DERWENT	AND	ON	2007/03/19 10:48
S1	2669	nephrotoxicity	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:51

EAST Search History

S2	120	estradiol adj metabolite	US-PGPUB; USPAT; EPO; DERWENT	ADJ	ON	2006/09/08 15:17
S3	4	S1 and S2	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/08 15:22
S4	602	2-hydroxyestradiol or 2-methoxyestradiol or 4-hydroxyestradiol or 4-methoxyestradiol	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/08 15:22
S5	602	2-hydroxyestradiol or 2-methoxyestradiol or 4-hydroxyestradiol or 4-methoxyestradiol	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/09/08 15:23
S6	12	S1 and S5	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/11 13:05
S7	5332	nephrotoxicity or proteinuria	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/08 15:27
S8	17	S7 and S5	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/08 15:27
S9	15338	nephrotoxicity or nephropathy or proteinuria	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/11 13:13
S10	602	2-hydroxyestradiol or 2-methoxyestradiol or 4-hydroxyestradiol or 4-methoxyestradiol	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/09/11 13:05
S11	50	S9 and S10	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/11 13:06
S12	21573	nephrotoxicity or nephropathy or proteinuria or kidney adj disease	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/09/11 13:13
S13	72	S12 and S10	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/09/11 13:13

EAST Search History

S14	8092	controlled adj release adj formulation	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:51
S15	607	2-hydroxyestradiol or 2-methoxyestradiol or 4-hydroxyestradiol or 4-methoxyestradiol	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2006/09/14 08:51
S16	32	S14 and S15	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:52
S17	14661	estradiol	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:52
S18	377	S14 and S17	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:52
S19	187	S14 and S17 @py<="2003"	US-PGPUB; USPAT; EPO; DERWENT	AND	ON	2006/09/14 08:52